Streptococcus anginosus ("Streptococcus milleri"): The Unrecognized Pathogen

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INTRODUCTION

The epithet "Streptococcus milleri," though not included in the approved lists of bacterial names (70), has been used to describe a bewildering assortment of streptococci associated with serious pyogenic infections. Three biotypes, four Lancefield antigens, and three hemolytic reactions can be recognized in isolates described as "S. milleri." In the past 15 years, the status of the taxonomy and nomenclature of these organisms has been debated, with some bacteriologists favoring unification of these heterogeneous streptococci into a single species and others advocating their separation into multiple species. The recent publication (17) of a comprehensive study of genetic relatedness among these organisms has established that they should be included in a single species officially named Streptococcus anginosus. Thus the name "S. milleri" as used in my review applies to a heterogeneous group of streptococci which are now officially called S. anginosus. Because of the variable bacteriological characteristics of these organisms and the emergence of multiple nomenclature schemes for them, their clinical significance, though well documented, is probably underrated. A beta-hemolytic "S. milleri" strain with Lancefield group C antigen would, according to current convention, be identified as a beta-hemolytic group C streptococcus. Unfortunately this designation includes a heterogeneous group of streptococci which are not necessarily "S. milleri." Nonhemolytic strains of "S. milleri" are likely to be identified only as viridans streptococci, which are generally considered nonpathogens. Such incomplete identifications may provide useless if not misleading information for the treatment of seriously ill patients. In light of the clinical significance of "S. milleri" and the difficulties associated with its recognition by bacteriologists, this review presents the salient bacteriological, taxonomic, and nomenclatural features of streptococci known as "S. milleri" and emphasizes their importance as etiologic agents of infectious disease.

BACTERIOLOGY OF "S. MILLERI"

The Concept of "S. milleri" as a Species

Like many clinically important bacterial groups, the streptococci have historically been classified and identified with the aid of a few characteristics which are easily determined by laboratorians. For streptococci, action on blood agar and serological traits were thought to suffice for classification. However, when a larger array of characteristics is examined, it becomes apparent that for some streptococci, hemolysis and serological reactions are not the inviolable indicators of relatedness they were once considered. The concept of "S. milleri" as a species is a primary example of this phenomenon.

Guthof (31) first used the name "S. milleri" in 1956 in reference to nonhemolytic streptococci isolated from oral infections. The species name was chosen to honor the oral microbiologist W. D. Miller. Colman and Williams (15) subsequently proposed the inclusion of Guthof's strains along with nonhemolytic isolates described by Ottens and Winkler (57) and the "Streptococcus MG" of Mirick and co-workers (53) in the species "S. milleri." These organisms shared common physiological characteristics and cell wall compositions. Despite these similarities, Colman and Williams noted that their "S. milleri" strains were serologically heterogeneous and evidenced Lancefield group A, C, F, or G antigen, various type antigens, or no detectable antigen. The physiological traits of Lancefield group A, C, and G nonhemolytic "S. milleri" strains differed significantly from those of their beta-hemolytic pyogeneslike counterparts, Streptococcus pyogenes. Streptococcus equisimilis, and largecolony group G streptococci. Conversely, Colman and Williams found that nonhemolytic "S. milleri" strains were

physiologically similar to the minute beta-hemolytic streptococci described by Long and Bliss (46) and shown by Bliss (10) to possess Lancefield group F or G antigen. Colman and Williams suggested that the "S. milleri" designation could also be applied to these beta-hemolytic strains.

In light of traditional streptococcal classification, the concept of the species "S. milleri" proposed by Colman and Williams was novel: they included serologically diverse isolates with various hemolytic reactions in a single species defined by physiological similarities. As discussed below, an alternative view promulgated by Facklam (26, 27) favored the separation of "S. milleri" into a number of distinct species, thus giving rise to dual systems of nomenclature for these streptococci. While Facklam's nomenclature is generally used in the United States, British and European authors usually prefer the "S. milleri" designation. Recently the unification of the various types of streptococci known as "S. milleri" into a single species has been proposed by Covkendall and associates (17) on the basis of deoxyribonucleic acid (DNA) hybridization studies. Since S. anginosus is the oldest approved name for these streptococci, it was suggested as the official name for organisms previously known as "S. milleri."

Physiological Characteristics

Regardless of nomenclature, organisms referred to as "S. milleri" share a core of physiological traits. The majority of isolates produce acetoin from glucose (7, 15, 58); ferment lactose, trehalose, salicin, and sucrose; and hydrolyze esculin and arginine (7, 15, 26, 58). In a study of more than 300 "S. milleri" isolates, Ball and Parker (7) were able to identify two minor groups whose characteristics differed slightly from those of the majority of strains. Isolates of one of the minor groups lacked some of the biochemical abilities of the major group and were more often beta-hemolytic and groupable with Lancefield group A, C, F, or G antiserum. The second minor group was found to have extended biochemical activities, fermenting raffinose and melibiose or mannitol. These organisms were usually nonhemolytic and nongroupable. Like physiological characteristics, colony morphology of "S. milleri" isolates is also variable. On blood agar, small colonies less than 0.5 mm in diameter are usually formed (7). Liu (45) noted smooth- and rough-colony variants in a strain of group F beta-hemolytic "S. milleri," and these colony types can also be observed with nonhemolytic isolates. Some authors (8, 36, 69) have remarked on a characteristic, caramellike odor produced by cultures of "S. milleri," but this is not a feature of all strains.

Carbon dioxide stimulates growth or is required for growth by some strains of "S. milleri" (7). The requirement of CO_2 , which could also be satisfied by oleic acid, was first noted in group F and G beta-hemolytic "S. milleri" or minute streptococci (19, 45). Later studies revealed nonhemolytic "S. milleri" isolates with similar properties. Sisson and co-workers (69) and Ball and Parker (7) have observed that "S. milleri" strains which require CO_2 for growth may be mistakenly referred to as "anaerobic" streptococci, since they grow well in an anaerobic environment but not in air without increased CO_2 .

Serological Characteristics

Both beta-hemolytic and nonhemolytic "S. milleri" strains with group A, C, F, G, or no detectable Lancefield antigen have been observed. Ottens and Winkler (57) dem-

onstrated that the group F antigen of nonhemolytic "S. milleri" strains was identical to that of beta-hemolytic group F isolates. They also noted the occurrence of carbohydrate-type antigens shared among group F, C, and G and nongroupable "S. milleri" strains. Lutticken and associates (48) described protein antigens which were present in a majority of 99 "S. milleri" isolates from pyogenic infections. They hypothesized that these proteins contribute to the pathogenicity of "S. milleri."

Among 259 non-beta-hemolytic "S. milleri" isolates studied by Ball and Parker (7), 4, 5, 4, and 1% carried Lancefield group A, C, F, or G antigen, respectively. Of 286 nonhemolytic organisms described by Facklam (26) which correspond to "S. milleri," 4, 3, 21, and 2% produced group A, C, F, or G antigen, respectively. Beta-hemolytic "S. milleri" strains seem to display a higher frequency of Lancefield antigen production. Of 87 beta-hemolytic strains examined by Ball and Parker, 8% were group A, 9% were group C, 47% were group F, and 5% were group G. Of 131 beta-hemolytic isolates examined by Poole and Wilson (60), 6% were group A, 22% were group C, 45% were group F, and 12% were group G. It should be noted that many species of viridans streptococci elaborate these or other Lancefield antigens (26); Lancefield serology is of little value in the classification and identification of these organisms. However, it does appear that, as a general rule, the majority of minute-colonyforming beta-hemolytic streptococci with group A, C, F, or G antigen are physiologically identical to "S. milleri" (42, 67).

Hemolytic Reactions

As mentioned above, streptococci classified as "S. milleri" may be beta-hemolytic or nonhemolytic. Included among the nonhemolytic strains are those that produce greening or the alpha reaction on blood agar. Of isolates examined by Ball and Parker (7), 56% were nonreactive, 19% were alpha reacting, and 25% were beta-hemolytic. Facklam (26), who examined only non-beta-hemolytic strains, found 56% to be nonhemolytic and 44% to produce the alpha reaction. Some beta-hemolytic "S. milleri" isolates produce reactions that may be interpreted as greening when surface colonies are examined. Clear-cut beta-hemolysis is observed if subsurface growth is examined (67).

Susceptibility to Antimicrobial Agents

Organisms classified as "S. milleri" are usually resistant to bacitracin and nitrofurazone (7, 60). Bacitracin resistance is a characteristic which allows separation of "S. milleri" isolates with the group A Lancefield antigen from bacitracinsusceptible S. pyogenes. Most strains studied have been found to be susceptible to penicillin (11, 60, 68, 73), ampicillin (11, 68), erythromycin, and tetracycline (60, 68). Penicillinase-resistant penicillins (nafcillin and methicillin), cephalothin, cefamandole, rifampin, vancomycin, clindamycin, and chloramphenicol are also effective in vitro against "S. milleri" (11, 68). Bourgault and co-workers (11) found that the aminoglycosides gentamicin and netilmicin were much more active against "S. milleri" than amikacin and kanamycin, but aminoglycosides were rarely bactericidal at concentrations safely attainable in serum. Sulfonamides are ineffective against "S. milleri" (73).

Nomenclature of "S. milleri"

In view of the heterogeneous serology, hemolytic behavior, and, to some extent, physiological characteristics of

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organisms referred to as "S. milleri," it is not surprising that these streptococci have been known by a variety of names. Andrewes and Horder in 1906 (1) first used the term S. anginosus to describe organisms found in the throats of patients with pharyngitis and in the normal alimentary canal: this designation was eventually used to describe beta-hemolytic "S. milleri" organisms belonging to Lancefield group F and group G type I (20). These organisms are the minute beta-hemolytic streptococci of Long and Bliss (46). In 1944, Mirick and associates published a series of papers on "Streptococcus MG," a nonhemolytic streptococcus isolated from patients with primary atypical pneumonia (53). Willers and co-workers (78) later demonstrated that "Streptococcus MG" produced group F antigen as well as a type antigen associated with some group F strains. Colman and Williams (15) were the first to propose that all the organisms mentioned above and the nonhemolytic group F. C. or G streptococci isolated from root canal cultures by Ottens and Winkler (57) were indeed related and similar to those described as "S. milleri" by Guthof (31). In addition, the Streptococcus intermedius (formerly Peptostreptococcus intermedius) and Streptococcus constellatus (formerly Peptococcus constellatus) species described by Holdeman and Moore (35) as anaerobic to aerotolerant streptococci appear to be physiologically similar to isolates described as "S. milleri." Since the proposal of the species "S. milleri" by Colman and Williams (15) in 1972, numerous other authors (7, 12, 32, 33, 50, 58, 79) have advocated its acceptance.

In 1977, Facklam (26) proposed that isolates referred to as "S. milleri" be divided, chiefly on the basis of lactose fermentation, into two species: "Streptococcus MG-intermedius" (lactose fermenting) and "Streptococcus anginosus-constellatus" (unable to ferment lactose). Facklam's study did not include beta-hemolytic "S. milleri" strains. Facklam recently revised his nomenclature for "S. milleri" to include beta-hemolytic forms and to use approved bacterial nomenclature (27). In his current system of nomenclature, lactose-positive "S. milleri" is called S. intermedius. Lactose-positive isolates which are capable of fermenting a wider than usual array of carbohydrates (7, 62, 65) are referred to as mannitol-positive S. intermedius. The lactosenegative "S. milleri" strains are currently called S. constellatus by Facklam, and beta-hemolytic strains are referred to as S. anginosus followed by their Lancefield group designation if any antigen is present. Table 1 summarizes the nomenclature schemes discussed above and correlates them with distinct subgroups of "S. milleri" described by Ball and Parker (7).

The most recent development in "S. milleri" nomenclature was the publication of an emended description of S. anginosus by Coykendall and co-workers in 1987 (17). The emended description, contained in a paper examining genetic relationships of "S. milleri" organisms, establishes S. anginosus as the approved name for all biotypes of organisms unofficially referred to as "S. milleri."

Taxonomy of "S. milleri"

Taxonomic studies, the logical foundation for nomenclature, have examined "S. milleri" organisms by a variety of methods. Taxonomic studies with manual compilation of data and perhaps subjective interpretation have been carried out by numerous authors (7, 15, 26, 33, 58) and have led to the dual schemes of nomenclature mentioned above. Computer-assisted numerical taxonomy studies by Bridge and Sneath (12), Colman (14), and Lutticken and associates (48) found that streptococci identified as "S. milleri" formed tight clusters when examined by the more impartial numerical classification methods. In studies of the cellular fatty acid composition of "S. milleri" strains, Labbe and colleagues (41) reported homogeneity in fatty acid profiles despite diverse physiological characteristics of the strains examined, while Drucker and Lee (23) were able to correlate biotypes of "S. milleri" strains with various fatty acid profiles.

Attempts to clarify the taxonomic status of "S. milleri" by the examination of genetic relatedness among strains have produced conflicting results. Drucker and Lee (24) examined the guanine-plus-cytosine content of "S. milleri" strains and found evidence of genetic heterogeneity, but early studies employing DNA hybridization techniques suggested that "S. milleri" strains with different physiological, serological, and hemolytic characteristics were closely related. Welborn and co-workers (77) provided hybridization data supporting the relatedness of type strains of S. constellatus and S. intermedius with Lancefield group F antigen strains that were beta-hemolytic or nonhemolytic. Kilpper-Balz and Schleifer (37), using techniques of DNA-ribosomal ribonucleic acid and DNA-DNA hybridization, found a cluster of strains, including the type strains of S. anginosus and S. intermedius, "Streptococcus MG," and minute beta-hemolytic group F and G streptococci. These strains also shared the

TABLE 1. Correlation of types of "S. milleri" isolates described by Ball and Parker (7) with nomenclature originally proposed and later revised by Facklam (26, 27)

	Nomenclature proposed by Facklam	
"S. milleri" characteristics"	"S. milleri" characteristics"	1984 ^c
Central group; non-beta-hemolytic; produce acetoin, hydrolyze arginine and esculin, and ferment lactose, trehalose, salicin, and sucrose	S. MG-intermedius	S. intermedius
Resemble central group but able to ferment additional sugars, usually raffinose and melibiose or mannitol	Not recognized	Mannitol-positive S. intermedius
Resemble central group but unable to ferment lactose	S. anginosus-constellatus	S. constellatus
Beta-hemolytic; often carry Lancefield group antigen and often lack one or more of the physiological characteristics of the central group	Not recognized	S. anginosus group A, C, F, or G or no group

^a As described by Ball and Parker (7).

^b Reference 26.

c Reference 27.

same peptidoglycan type. A close relationship between the type strain of *S. anginosus* (a beta-hemolytic group G isolate) and minute hemolytic streptococci of group A, C, F, or G or with no detectable serogroup was demonstrated via hybridization studies by Ezaki and colleagues (25). Farrow and Collins (30) demonstrated a close genetic relationship between the type strains of *S. anginosus*, *S. constellatus*, and *S. intermedius*.

To examine genetic relatedness among members of the "S. milleri" group in more depth, Kilpper-Balz and associates (38) carried out DNA-DNA hybridization experiments under both optimal and stringent conditions by varying the formamide concentration in hybridization mixtures. Optimal and stringent conditions in their experiments corresponded respectively to 25 and 10°C below the thermal melting point of DNA. The decreased hybridization levels observed under stringent conditions led these authors to conclude that type strains of S. anginosus, S. constellatus, and S. intermedius form separate species and that S. intermedius is more closely related to S. constellatus than to S. anginosus. Of the eight isolates they examined which had been phenotypically identified as "S. milleri," five were related at the species level to S. constellatus and three were related to S. anginosus.

Recently Coykendall and co-workers (17) examined a collection of 40 "S. milleri" strains with various hemolytic, serological, and physiological characteristics. They measured DNA-DNA hybridization under optimal (48°C) and stringent (57°C) conditions. Unlike Kilpper-Balz and associates, the Coykendall group found no significant reduction in hybridization levels under stringent conditions. As pointed out by Coykendall and colleagues, the formamide method employed by Kilpper-Balz and co-workers may be so stringent that it reveals heterogeneities that are undetected by the membrane filter and S1 nuclease methods employed by other workers. On the basis of the data generated in their study, Coykendall and associates concluded that the phenotypically heterogeneous isolates of streptococci they examined were similar enough genetically to be included in a single species. They noted that S. anginosus, originally described by Andrewes and Horder (1), is the oldest accepted name applied to members of the "S. milleri" group. They therefore provided an emended description of S. anginosus which accommodates strains with the various hemolytic, serological, and physiological traits of streptococci known as "S. milleri." Publication of this emended description (17) established S. anginosus as the approved name for this group of bacteria.

CLINICAL SIGNIFICANCE OF "S. MILLERI"

Habitats of "S. milleri"

Isolation of "S. milleri" from a variety of body sites suggests that it is a common commensal organism in humans. Cultures of the oral cavity (50), throat (8, 47), feces (71, 75), and vagina (80) have all yielded "S. milleri" strains. Poole and Wilson (62) noted that a majority of isolates from teeth were hemolytic, but fecal and vaginal strains tended to be nonhemolytic. Most of the vaginal strains, unlike other "S. milleri" isolates, produced acid from raffinose and melibiose. This biotype, which corresponds to mannitol-positive S. intermedius in Facklam's nomenclature (27), is isolated frequently from the urine cultures of female patients and ferments mannitol in addition to raffinose and melibiose (65). Except for the notable association between this "S. milleri" biotype and the female genital tract, there seems to

be no well-established relationship between hemolytic, serological, and physiological characteristics and the site of isolation.

"S. milleri" in Infections

The first description of "S. milleri," by Guthof (31), dealt with strains isolated from oral infections, and subsequent studies have confirmed the participation of these organisms in the pathogenesis of infections of the mouth and teeth (18, 57, 79). Drucker and Green (22) provided evidence for the cariogenic potential of "S. milleri," although the strains they examined were not as cariogenic as Streptococcus mutans.

The pathogenic potential of "S. milleri" in throat and respiratory infections is not well established. In generally accepted methods for screening throat and respiratory cultures for pathogenic streptococci, only beta-hemolytic isolates are usually deemed worthy of identification. "S. milleri" is commonly found among beta-hemolytic streptococci from these sources (13, 42, 67). While Poole and Wilson (60) present some evidence for the participation of beta-hemolytic "S. milleri" in pharyngitis, Bucher and Von Graevenitz (13) argue that further data are required to confirm the pathogenicity of these organisms in the throat.

"S. milleri" plays an important role in infections of internal organs and certain body fluids. In a study of bacteria isolated from abscesses of the central nervous system, DeLouvois (21) found "S. milleri" to be the most frequent isolate from intracranial pus. "S. milleri" has been implicated in other reports as a cause of brain abscess (51) and meningitis (39, 72). "S. milleri" also functions as a pathogen in pyogenic liver abscess (9, 40, 54, 59) and appendicitis (49, 61). Mannitol-fermenting "S. milleri," frequently isolated from the female genital tract, has been implicated in two cases of neonatal sepsis (16). Although it is not a common isolate among streptococci causing endocarditis and bacteremia (44, 52, 55, 58; E. L. Rank, R. Phee, and J. Wilson, Clin. Microbiol. Newslett. 6:52-54, 1984), "S. milleri" in the blood should alert clinicians to the possible existence of an abscess functioning as the source of bacteremia (2, 55).

Parker and Ball (58) studied the streptococci (excluding pneumococci) isolated from infected blood, cerebrospinal fluid, and internal organs of patients in Britain during 1972 to 1974. They found that "S. milleri" accounted for 10% of the 809 streptococcal isolates studied and for about 30% of the streptococci found in purulent infections in internal organs. A number of other studies have surveyed the distribution of "S. milleri" in various types of clinical specimens (52, 55, 60, 68, 76). These reports confirm that "S. milleri" participates in infections in a variety of body sites, as outlined in the specific examples above. The major common finding in these studies is the association of "S. milleri" with pyogenic infection and abscess formation. The proclivity of these organisms for involvement in pyogenic infections, though well documented, remains largely unexplained.

Possible Pathogenic Mechanisms of "S. milleri"

Extracellular enzymes which may contribute to pathogenic potential have been found in isolates of "S. milleri." Colman and Williams (15) noted that hyaluronidase was more commonly elaborated by beta-hemolytic group F "S. milleri" than by nonhemolytic strains. Poole and Wilson (62) found that this observation also held true for group A and C beta-hemolytic "S. milleri." In a study of CO₂-dependent streptococci, Pulliam and associates (63) found that 33% of

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69 isolates that could be classified as "S. milleri" elaborated extracellular deoxyribonuclease. In addition to these enzymes, which may play some role in pathogenicity, organisms classified as "S. milleri" have been observed to produce extracellular products with immunosuppressive effects (5, 6, 34).

Tresadern and associates (74) have hypothesized that prophylactic use of antibiotic combinations such as gentamicin and metronidazole for surgical patients may enhance infection caused by "S. milleri." They described a group of patients treated either prophylactically or after development of sepsis caused by mixed fecal flora. They proposed that "S. milleri" of fecal origin could, by overgrowth of suppressed gram-negative organisms, establish itself as a pathogen. Persistence of "S. milleri" after metronidazole treatment of experimental abscesses caused by Bacteroides fragilis and "S. milleri" has been observed in an animal model (56).

Although often isolated in pure culture, "S. milleri" can be found in polymicrobial infections (44, 54, 68, 76, 79). This raises the possibility of synergistic infections involving S. milleri, but this phenomenon has yet to be investigated.

Lebrun and colleagues (43) recently demonstrated the absence of receptors for the Fc fragment of human immunoglobulin G on cells of beta-hemolytic group C "S. milleri" strains isolated from throat cultures. Strains of large-colony beta-hemolytic group C streptococci (S. equisimilis) from throat cultures produced this receptor, which is hypothesized to be a virulence factor. They also found that organisms with the Fc receptor were associated with pharyngitis, while the majority of the "S. milleri" strains examined were not. Thus this study seems to rule out the presence of at least one type of possible virulence factor in group C beta-hemolytic "S. milleri" strains isolated from human throats.

Problems with Recognition of "S. milleri" as a Pathogen

Diverse serological and hemolytic reactions along with the tumultuous nomenclatural history of organisms called "S. milleri" have created problems for clinical microbiologists charged with the task of identifying these pathogens. In accordance with current methodology, a beta-hemolytic "S. milleri" isolate would probably be identified only as a beta-hemolytic streptococcus with a given Lancefield antigen, while a nonhemolytic "S. milleri" isolate might be identified simply as a viridans streptococcus. To identify hemolytic or nonhemolytic streptococci as "S. milleri," physiological tests, often considered too time-consuming or expensive, must be carried out on the isolates. Thus many "S. milleri" strains are incompletely identified and erroneously considered clinically insignificant. In addition to identification schemes employing tubed and plated media (26, 58), other more convenient methods are commercially available for the identification of "S. milleri" (3, 4, 28, 29, 66). For presumptive identification of beta-hemolytic "S. milleri," Bucher and Von Graevenitz advocate use of a rapid method for determining acetoin production (13). This test, along with rapid tests for arginine hydrolysis and sorbitol fermentation, can be used to presumptively separate nonbeta-hemolytic "S. milleri" strains from other viridans streptococci (64). In view of the importance of "S. milleri" as a pathogen, laboratorians should make efforts to identify this organism, even if only via presumptive tests.

CONCLUSIONS AND FUTURE PROSPECTS

Organisms referred to as "S. milleri," which are now correctly called S. anginosus, are frequently incompletely

identified because of their diversity of standard characteristics (serological and hemolytic) for streptococcal identification and because of confusion surrounding their taxonomy and nomenclature. Lack of recognition of these clinically significant streptococci can lead to mismanagement of patients with life-threatening infections. The importance of these organisms as pathogens mandates increased efforts by clinical laboratorians towards their accurate identification. While publication of an emended description of S. anginosus (17) establishes this name as the approved species name for organisms popularly called "S. milleri," confusion over nomenclature will undoubtedly persist. The pathogenic mechanisms of "S. milleri" and possible associations between given biotypes and specific kinds of infection need to be explored further. Such studies will ensure the appreciation and enhance the recognition of the clinically important streptococci known as "S. milleri."

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